Proposed Decision Memo for Intracranial Stenting and Angioplasty (CAG-00085R5)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) has reviewed the evidence for intracranial stenting and angioplasty for the patients with intracranial atherosclerotic disease (ICAD), who are medically refractory to therapy in intracranial vessels with ≥50% artery lumen stenosis that are accessible to the system. We propose to make no change to section 20.7.B.5 of the National Coverage Determination Manual titled “Percutaneous Transluminal Angioplasty” (PTA).

We are requesting public comments on this proposed determination pursuant to section (§) 1862(l) of the Social Security Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File:(CAG-00085R5)
Proposed Decision Memorandum for Intracranial Stenting and Angioplasty

FROM:

Steve E. Phurrough, MD, MPA
Director, Coverage and Analysis Group

Marcel Salive, MD, MPH
Director, Division of Medical and Surgical Services

Sandy Jones, RN, MS
Lead Analyst

Joseph Chin, MD
Lead Medical Officer

SUBJECT: Proposed Decision Memorandum for Intracranial Stenting and Angioplasty
DATE: February 14, 2008

I. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) has reviewed the evidence for intracranial stenting and angioplasty for the patients with intracranial atherosclerotic disease (ICAD), who are medically refractory to therapy in intracranial vessels with ≥ 50% artery lumen stenosis that are accessible to the system. We propose to make no change to section 20.7.B.5 of the National Coverage Determination Manual titled “Percutaneous Transluminal Angioplasty” (PTA).

We are requesting public comments on this proposed determination pursuant to section (§) 1862(l) of the Social Security Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

II. Background

Intracranial angioplasty and stenting is a relatively novel approach for the treatment of refractory, symptomatic intracranial artery stenosis. CMS issued a national coverage determination on intracranial PTA and stenting, §20.7.B.5 of the Medicare National Coverage Determination Manual, in January 2007. Our final decision memorandum, dated November 6, 2006 describes the background, earlier history of coverage and analyzes evidence available up to that time (see: http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=177). We are incorporating the final decision memorandum as part of the record of this proposed decision memorandum.[1]

In August 2007, CMS accepted a formal request from Boston Scientific Corporation to reconsider coverage for intracranial stenting and angioplasty using the Wingspan® Stent System with Gateway™ Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter for the treatment of intracranial arterial stenosis ≥ 50%.

III. History of Medicare Coverage

Effective November 2006, the Medicare National Coverage Determination (NCD) Manual (20.7.B.5) for PTA states stenting of the intracranial arteries has been conditionally covered to treat cerebral artery stenosis as follows.

"Medicare covers PTA and stenting of intracranial arteries for the treatment of cerebral artery stenosis ≥ 50% in patients with intracranial atherosclerotic disease when furnished in accordance with the [Food and Drug Administration] FDA- approved protocols governing Category B [Investigational Device Exemption] IDE clinical trials. CMS determines that coverage of intracranial PTA and stenting is reasonable and necessary under these circumstances."[2]

Benefit Category

Medicare is a defined benefit program. A prerequisite for Medicare coverage is that an item or service must meet one of the statutorily defined benefit categories in the Social Security Act and not otherwise be excluded from coverage. Intracranial stenting and angioplasty at a minimum, falls under the benefit category set forth in §1861(b)(3) (inpatient hospital services), a part A benefit under §1812(a)(1) and §1861(s)(1) (physician services), a part B benefit.

IV. Timeline of Recent Activities

August 24, 2007	CMS accepts Boston Scientific Corporation’s formal NCD reconsideration request for expanded coverage of intracranial stenting and angioplasty. The tracking sheet is posted and the initial 30-day comment period begins.
September 18, 2007	CMS met with Boston Scientific Corporation’s staff to discuss their proposed observational clinical study for consideration under coverage with evidence development.
September 23, 2007	Initial 30 day public comment period closes. Comments are posted on the website.
January 7, 2008	CMS received Boston Scientific Corporation’s revised observational study.
February 14, 2008	PDM is posted and the second 30-day public comment period begins.

V. FDA Status

Congress has designated the FDA responsibility for review and approval of Humanitarian Use Devices (HUDs) that are used to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States. A Humanitarian Device Exemption (HDE) allows the HUD device to be marketed for a specific condition. The device manufacturer must submit an humanitarian device exemption (HDE) application, which is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

The HDE holder must ensure that an approved HUD is only used when there are Institutional Review Board (IRB) approvals and continuous reviews. Also, the HUD applicant must assure the costs of the device do not exceed the costs of research, development, manufacturing and distribution of the device. Finally, to maintain a HUD status, the FDA may require annual device utilization reports. [3]

On August 3, 2005, the FDA, Center for Devices and Radiological Health (CDRH), reviewed Boston Scientific Corporation's application for the Wingspan® Stent System with Gateway™ PTA Balloon Catheter and approved this micro-catheter based delivery system as a HDE used for the treatment of medically refractory ICAD to improve the intracranial vasculature accessible to this device in symptomatic patients with $\geq$ 50% stenosis. The FDA letter[4] refers to this application submitted by Boston Scientific Corporation and the public was notified of this FDA decision.[5] Based on the data submitted with the HDE application, the Gateway™ PTA Balloon Catheter Stent System will not expose patients to an unreasonable or significant risk of illness or injury. Additionally, when the device is used following the instructions for use, it has been determined that there is a probable benefit to health that outweighs the risks of illness or injury.

CMS does not have a national policy that addresses coverage of HUDs. Currently, contractors have the discretion to provide coverage for these devices in the absence of a national coverage determination. A HUD is nationally not covered if it falls under the purview of an NCD which nationally non-covers the device or service for which the HUD may be used.

VI. General Methodological Principles

When making national coverage decisions, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Coverage Advisory Committee, evidence-based guidelines, professional society position statements, expert opinion and public comments. The critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific clinical questions relevant to the coverage request can be answered conclusively; and 2) the intervention will improve patients' net health outcomes. (The General Methodological Principles of Study Design is located in *Appendix A*.)

We, generally, divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

Public comments sometimes cite the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as results of individual practitioners or patients are less rigorous and therefore less useful when making a coverage determination. Public comments that contain personal health information will not be made available to the public. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

In this reconsideration, we considered studies and evidence that were published after the prior decision that addressed intracranial angioplasty and stenting in 2006. Health outcomes of interest include mortality, stroke, adverse events and restenosis (development of a new obstructive lesion in the treated segment). Although often reported, the ability to successfully perform the stenting and angioplasty or the ability to increase the intracranial artery lumen diameter are not sufficient outcomes by themselves. These outcomes indicate the feasibility of applying the intervention; however, while a necessary first step, procedural outcomes do not provide evidence on the health outcomes of interest to CMS.

Literature Search

CMS searched PubMed (2006 to present) for publications of randomized clinical trials (RCTs), observational studies and reviews on intracranial stenting and angioplasty. General keywords included intracranial, stenting, angioplasty and Wingspan®. Studies must have presented original data and been published in peer-reviewed English language journals. After an initial scan of the literature that included other intracranial stent systems, our search was narrowed to include only studies that used the Wingspan® system since other stents were not self-expanding and have not been FDA approved for uses in the intracranial arteries. Abstracts and animal studies were excluded.

B. Discussion of evidence reviewed

1. Question

- Is the evidence sufficient to conclude that percutaneous transluminal angioplasty and stenting of symptomatic intracranial artery stenosis $\geq$ 50% improves health outcomes?

2. External technology assessments

We did not request an external technology assessment on this issue and are not aware of any other similar assessments.

3. Internal technology assessment

Bose A, Hartmann M, Henkes H, et al. A novel, self-expanding, nitinol stent in medically refractory intracranial atherosclerotic stenoses: the Wingspan study. Stroke 2007;38(5):1531-1537.

Bose and colleagues published the results of a case series of 45 patients “to assess the safety and performance of the Wingspan[®] stent system and Gateway[™] percutaneous transluminal angioplasty balloon catheter in the treatment of high-grade, intracranial atherosclerotic lesions in patients who had failed medical therapy.” Inclusion criteria included symptomatic intracranial atherosclerotic stenosis ≥ 50% in a vessel 2.5 to 4.5 mm in diameter, failed antithrombotic therapy, at least 7 days after stroke, and modified Rankin score ≤ 3. Exclusion criterion was pregnancy. Stenting and angioplasty were performed in 12 centers in Europe and Asia. Primary end points were “composite ipsilateral stroke/death at 30 days, stent success and procedure success.” Follow-up evaluations were at discharge, 30 days and 6 months. Mean age was 66 years. Men comprised 73% of the study population. Of the 45 patients, 42 had stroke as the qualifying event. Eighty percent were taking aspirin and 13% were taking warfarin.

The authors reported: “Among the 45 patients enrolled, the degree of stenosis was reduced from a baseline of 74.9 ± 9.8% to 31.9 ± 13.6% after stenting and 28 ± 23.2% at the 6-month follow-up. The 30-day composite ipsilateral stroke/death rate was 4.5% (2/44). At the 6-month follow-up, the ipsilateral stroke/death rate was 7.0%, the rate for all strokes was 9.7%, and all-cause mortality was 2.3%.” Percent restenosis ≥ 50% at 6 months was 7.5%. They concluded: “In medically refractory patients with high-grade intracranial atherosclerotic stenoses, a new treatment paradigm involving predilation with an undersized Gateway[™] percutaneous transluminal angioplasty balloon catheter and placement of a self-expanding Wingspan[®] stent system appears to be safe, may facilitate remodeling and may contribute to favorable angiographic outcomes.”

In this case series, the sample size was small. There was no control group. Long term outcomes were not available. All patients were placed on clopidogrel for 30 days after stenting and aspirin for life. The number of myocardial infarctions was not reported. The results of this study appear to have been included in the evidence reviewed by the FDA for the Wingspan® HDE approval and summarized in the FDA Summary of Safety and Probable Benefit for the Wingspan® Stent System (available at: http://www.fda.gov/cdrh/pdf5/h050001b.pdf).

Fiorella D, Levy EI, Turk AS, et al. US multicenter experience with the wingspan[®] stent system for the treatment of intracranial atheromatous disease: periprocedural results. Stroke 2007;38:881-887.

Fiorella and colleagues reported the results of the Wingspan® registry (case series) of 78 patients in the U.S. (4 centers) who were treated with the Wingspan® stent system. Of these, 48 (62%) patients presented with strokes. Fifty-nine patients (76%) had a history of antiplatelet therapy failure. Initial percent stenosis was presented in aggregate only, with 54 of 82 (66%) lesions having a 70% stenosis or greater. Stenting and angioplasty were performed in 4 U.S. centers. Mean age was 64 years. Men comprised 58% of the study population.

The authors reported 4 (5.1%) periprocedural deaths and 1 major stroke (1.2%). Postprocedural imaging showed that 34.2% (13/38) of patients had developed new ischemic lesions after the procedure. The authors stated: “At the same time, it is important to note that the periprocedural complications encountered during intracranial PTAS are typically very severe, with 4 of the 5 major complications in the current series resulting in patient death within 30 days.” They concluded: “Angioplasty and stenting for symptomatic intracranial atheromatous disease can be performed with the Gateway balloon–Wingspan stent system with a high rate of technical success and acceptable periprocedural morbidity. Our initial experience indicates that this procedure represents a viable treatment option for this patient population.”

In this case series, all patients received aspirin and clopidogrel before the procedures and for a minimum of 4 weeks after the procedures. Longer term follow-up (30 days or 6 months) was not reported. The number of myocardial infarctions was not reported. Outcomes were not independently adjudicated.

Levy EI, Turk AS, Albuquerque FC, et al. Wingspan[®] in-stent restenosis and thrombosis: incidence, clinical presentation and management. Neurosurgery 2007;61:644–651.

Levy and colleagues reported in-stent restenosis (ISR) and thrombosis rates for 78 patients in the Wingspan® registry. ISR was "defined as stenosis greater than 50% within or immediately adjacent (within 5 mm) to the implanted stents and absolute luminal loss greater than 20%." The authors reported: "To date, follow-up imaging (average duration, 5.9 mo; range, 1.5–15.5 mo) is available for 84 lesions treated with the Wingspan[®] stent (78 patients). Follow-up examinations consisted of 65 conventional angiograms, 17 computed tomographic angiograms, and two magnetic resonance angiograms. Of these lesions with follow-up, ISR was documented in 25 and complete thrombosis in four. Two of the 4 patients with stent thrombosis had lengthy lesions requiring more than one stent to bridge the diseased segment. ISR was more frequent (odds ratio, 4.7; 95% confidence intervals, 1.4–15.5) within the anterior circulation (42%) than the posterior circulation (13%). Of the 29 patients with ISR or thrombosis, eight were symptomatic (four with stroke, four with transient ischemic attack) and 15 were retreated. Of the retreatments, four were complicated by clinically silent in-stent dissections, two of which required the placement of a second stent. One was complicated by a postprocedural reperfusion hemorrhage."

The authors concluded: "The ISR rate with the Wingspan[®] stent is higher in our series than previously reported, occurring in 29.7% of patients. ISR was more frequent within the anterior circulation than the posterior circulation. Although typically asymptomatic (76% of patients in our series), ISR can cause neurological symptoms and may require target vessel revascularization." This case series reported findings from the Wingspan® registry, as did the Fiorella study above, and has the same potential methodological issues.

4. MedCAC

No MedCAC was convened on this issue.

5. Evidence-based guidelines

Not applicable.

6. Professional Society Position Statement

Higashida RT et al. Intracranial angioplasty and stenting for cerebral atherosclerosis: A Position Statement of the American Society of Interventional and Therapeutic Neuroradiology (ASITN), Society of Interventional Radiology (SIR), and the American Society of Neuroradiology (AJNR). Am J Neuroradiol 2005;26(9):2323-2327 and J Vasc Interv Radiol 2005;16(10):1281-1285.

In 2005, a multispecialty group published a position statement for the use of intracranial stenting and angioplasty for cerebral atherosclerosis. These societies favor coverage for intracranial angioplasty with or without stenting for intracranial atherosclerotic disease.

- For symptomatic patients with a ≥ 50% intracranial stenoses who have failed medical therapy, balloon angioplasty with or without stenting should be considered.
- Patients who have an asymptomatic intracranial arterial stenosis should first be counseled regarding optimizing medical therapy. There is insufficient evidence to make definitive recommendations regarding endovascular therapy in asymptomatic patients with severe intracranial atherosclerosis. They should be counseled regarding the nature and extent of their disease, monitored for new neurological symptoms and have periodic non-invasive imaging at regular intervals of 6-12 months (magnetic resonance angiography or computed tomographic angiography) initially, and then by cerebral angiography if warranted. At a minimum, optimal prophylactic medical therapy should be instituted, which might include antiplatelet and/or statin therapy.
- Continued evaluation and improvements in both pharmacological and catheter-based therapies are needed to reduce the stroke burden from intracranial atherosclerosis.
- Recommend reimbursement by third party insurers so that those patients may have access to such interventions.

The above professional society position statement is the same as we summarized in our previous intracranial stenting and angioplasty decision memorandum and the recommendations have not changed since our last decision.

7. Expert Opinion

CMS received in-depth comments from multiple professional societies who are committed to the care of intracranial atherosclerotic disease and intracranial stenting issues. With the exception of the joint professional society position statement provided in section 6 above, we provide highlights of the comments from each group in this section.

Comments from Professional Societies and Organizations

CMS received public comments from the following four groups: the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS); the Society of Interventional Radiology (SIR); the American Society of Neuroradiology (ASNR); and the Society of NeuroInterventional Surgery (SNIS) formerly known as the American Society of Interventional and Therapeutic Neuroradiology (ASITN).

Intracranial Stenting and Balloon Catheter PTA under CED

American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS): The AANS and CNS requested Medicare coverage under CED for the use of intracranial stenting and balloon catheter PTA. They cite:

“The U.S. Multi-center Wingspan[®] Stent System Registry data that indicates post procedural rates of mortality at 5.6% and stroke at 7.8%. Also, the AANS and CNS point to the Wingspan[®] HDE clinical study outcomes that show: a 97.7% procedural success rate and a one-year follow-up of symptomatic patients with ICAD of 50 percent or greater reveals the treated lesions are 90% free of stroke.”[6]

Further, the AANS and CNS requests an extension for the comment period for the intracranial stenting and angioplasty reconsideration to offer the community an opportunity to evaluate new data from the National Institutes of Health (NIH) funded clinical trial titled: “Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis” (SAMMPRIS). This is a new on-going clinical trial and results are not expected until after the closure of this reconsideration.

Medical and Surgical Therapies versus Cerebral Endoluminal Revascularization

The Society of Interventional Radiology (SIR): SIR favors Medicare coverage for intracranial stenting and angioplasty and references the Warafin versus Aspirin Symptomatic Intracranial Disease (WASID) clinical trial[7] results that indicate a higher risk of stroke for intracranial (IC) atherosclerotic stenosis when compared to extracranial (EC) atherosclerotic stenosis as well as describes the lack of effective treatment when using medical and surgical therapies. Additionally, SIR reports:

“intracranial artery angioplasty, with or without stenting, is safe and efficacious with improved patient stroke and death rates compared to best medical therapy and that there are durable results despite restenosis and repeat angioplasty is extremely successful in preventing stroke.”

SIR recognizes the lack of long-term stroke prevention data and reports there are only two clinical trials: “Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA) and the Wingspan[®] Trials[8] for endovascular therapy”. However, “according to case series, single and multi-center data, the benefits of balloon angioplasty alone shows both stroke prevention and patient survival”.[9] Using these same multi-center case series SIR cites: “a one year stroke/death rate of up to 23% in patients with greater than 70% intracranial stenosis treated with medical therapy”.[10] In comparison to the 23% rate of stroke and death when using medical therapy alone, stroke and death rates are lower when using angioplasty versus medical therapy.

“For the periprocedural (primary angioplasty) stroke and deaths, the annual stroke rate is 3.2% in the territory of treatment and there is a 4.4% annual rate for all strokes.”[11] Another published report reveals “when angioplasty alone was the treatment, the periprocedural stroke and death rate was 4.8% and the annualized stroke rate was 1.8% with the annualized stroke and all-cause death rate of 3.0% suggesting patient outcome health benefits”.[12]

Intracranial Stenting and Angioplasty for Symptomatic Patients and CED

The American Society of Neuroradiology (ASNR); the Society of Interventional Radiology (SIR) and the American Society of Interventional and Therapeutic Neuroradiology (ASITN): The ASNR, SIR and the ASITN submitted public comments that support intracranial stenting and angioplasty for symptomatic patients with a >70% intracranial stenosis.[13] In the past, these societies agreed that the risk of treatment using the existing technology combined with the poor understanding of the natural history of ICAD yielded an appropriate CMS non-coverage policy for intracranial stenting and angioplasty. However, now this group references outcome data that reveals “as many as half of the ICAD patients not responding to medication have a treatment failure within a median time of 36 days, with half of these therapeutic failures experiencing a major stroke or death within this timeframe”.[14] Reportedly, data suggests there may be a benefit to the use of stenting and angioplasty compared to the use of the best medical therapy for symptomatic 50-70% stenosis but that potential benefit remains debatable. These societies acknowledge the major medical advances in the last decade and the rates of stroke and death risks without the provision of ICAD treatment[15] and want to allow for the opportunity to secure robust effectiveness data for stroke prevention. As a result, based on a review of 2 prospective multi-center clinical trials and numerous individual reports over the last 20 years related to intracranial stenting and angioplasty, support is as follows:

1. "Medicare coverage for angioplasty and or stenting for symptomatic patients with greater than 70 percent intracranial arterial stenosis; and
2. Medicare coverage for intracranial angioplasty and stenting for other patients within the context of Category B investigational device exemption (IDE) trials under coverage with evidence development (CED) within a registry."

In addition to the comments received from the above multispecialties, the *Society of Vascular and Interventional Neurology* (SVIN); the *Society for Cardiovascular Angioplasty and Interventions* (SCAI); and the *American Academy of Neurology* (AAN) and the *American Society of Neuroradiology* (ASNR) submitted comments via email. Two of these societies support expanded Medicare coverage for stenting and angioplasty. The SVIN offers strong support and a consensus statement for coverage with evidence development CED for use of the Wingspan® Intracranial Stent for patients with $\geq$ 70% stenosis who have failed to improve risk factors using the best medical therapy. The SCAI urges CMS to conditionally expand coverage for restricted patient populations including patients with acute stroke who cannot have intravenous thrombolysis but who are eligible for endovascular approaches. Also, the SCAI recommends coverage for symptomatic patients with $\geq$ 50% ICAD stenosis or who are not able to take aspirin or who persist with TIA or stroke symptoms after receiving aspirin therapy. The AAN and the ASNR support the current Medicare coverage policy of intracranial stenting with angioplasty under an investigational device exemption (IDE) clinical trial.

The American Academy of Neurology (AAN) and the American Society of Neuroradiology (ASNR) provided a brief statement that opposes coverage of intracranial stenting and angioplasty under a CED registry. The basis of opposition to a national coverage decision under CED is that a “CED registry would seriously jeopardize the completion of any RCT [randomized controlled trial]”. Yet these groups support Medicare coverage of intracranial stenting and angioplasty under an IDE.

8. Public Comments

CMS received 15 public comments during the initial comment period. Seven of these 15 comments were from professional societies that have been described in section 7 above and the remaining 8 were general public comments described in this section. Eight commenters cited 64 references. References not specifically addressed in this or the previous decision memorandum were determined to be outside the scope of this reconsideration because they evaluated devices other than the FDA approved intracranial stent or included no relevant data. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

General Public Comments

Eight of the remaining 15 public comments came from: 7 physicians and 1 director of a health system. CMS received no comments from patients.

Comments with Evidence

Four of the 8 commenters advocate for the expansion of CMS' current policy of Intracranial Stenting and Angioplasty based on evidence that comes from small, uncontrolled case series that lack long term follow-up. Most of the commenters referenced evidence that focused on the safety and performance of the device. There were no comments on the availability of an accessible vessel for the stenting system. One commenter stated that based on the WASID data there is "no data to suggest that Wingspan[®] is worse than the natural history for this patient subgroup [symptomatic patients with ≥ 70% stenosis] only studies that show benefit in the high risk group". With limited long term results and evidence using comparator groups for either optimal medical therapy or stenting and angioplasty, there is room for uncertainty about conclusions related to treatment methodologies and improved health outcomes for the Medicare population. Three commenters support expanded Medicare coverage for intracranial stenting and angioplasty for patients with symptomatic ≥ 70% stenosis stating, "there is no good open surgical alternative". Also, these commenters note that health outcomes for patients "using medical therapy alone indicates a 22% first-year stroke rate" or "dismal outcomes". One commenter acknowledges there are too few patients to create a strong evidence base for stenting superiority compared to medical therapy but urges expanded coverage "especially for those who are experiencing multiple TIAs on coumadin[®] and plavix[®]".

There is a newly funded clinical trial titled "Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)" designed to determine health outcomes comparing optimal medical therapy to stenting and includes a 2 year mean follow-up. One commenter requests an extension of the public comment period to permit stakeholders an opportunity to evaluate data from the SAMMPRIS trial. We await the results from this study.

Comments without Evidence

Four of the 8 commenters do not reference evidence. All 4 of these commenters support Medicare coverage for stenting and angioplasty and 1 of the 4 commenters favors angioplasty with or without stenting. One physician states “there is good evidence intracranial angioplasty and stenting for patients who are symptomatic with ≥ 70% stenosis decreases the risk of stroke”. In contrast, another commenter strongly urges coverage for intracranial angioplasty with or without stenting for symptomatic patients with arterial intracranial stenosis ≥ 70%. Two commenters acknowledge there is little patient experience but we frequently treat patients with rare disorders and this procedure is a method to decrease or prevent strokes. One commenter recommends coverage only when the procedure is included in a registry or trial while another commenter stipulates the inclusion of caveats for institutional criteria and physician credentialing.

Costs

Three commenters with evidence and 1 commenter without evidence remarked about the cost of intracranial stenting. CMS does not consider costs in making national coverage determinations.

Public comments can be located on our coverage website at:

http://www.cms.hhs.gov/mcd/viewpubliccomments.asp?nca_id=214

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act §1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member,” §1862(a)(1)(A).

We previously found that PTA and stenting of intracranial arteries for the treatment of cerebral artery stenosis ≥ 50% in patients with intracranial atherosclerotic disease when furnished in accordance with the FDA-approved protocols governing Category B IDE clinical trials was reasonable and necessary under §1862(a)(1)(A).

The previous CMS decision was restricted to PTA and stenting and this reconsideration request includes angioplasty with stenting; therefore, we are not addressing PTA without stenting in this proposed decision.

Our analysis focused on the following question:

- Is the evidence sufficient to conclude that percutaneous transluminal angioplasty and stenting of symptomatic intracranial artery stenosis ≥ 50% improves health outcomes?

Since our prior decision on intracranial PTA and stenting in November 2006, 3 studies (Bose, Fiorella, Levy) have been published that presented data using the Wingspan® stent system. The study by Bose presented data that appears to have been the basis for the FDA decision and summary of safety and probable benefit (see: http://www.fda.gov/cdrh/pdf5/h050001b.pdf). Although the data were not published at the time, this evidence was considered in our November 2006 decision and is not considered new evidence for this reconsideration.

The Fiorella and Levy studies presented data from the Wingspan® registry of 78 patients. These studies, as with all case series type studies, are difficult to interpret without additional studies that reduce the possibility of inherent biases and substantiate the clinical findings. Various biases may have been factors in the observed differences in the registry data compared to the initial Wingspan® study presented by Bose. Levy and colleagues reported: “The ISR (in-stent restenosis) rate with the Wingspan[®] stent is higher in our series than previously reported, occurring in 29.7% of patients.” In addition, the lack of control groups and long term follow-up add to the uncertainty of clinical benefit. We are concerned that Levy et al. considers in-stent dissections to be “clinically silent,” particularly in view of their treatment with a second stent. Concerns were also noted by Kallmes and Cloft (Kallmes 2008) who reported: “The overall restenosis rate in the study by Levy et al. was 31%, even though they excluded 4 cases of complete occlusion. Including those cases of complete occlusion would have increased the reported rate of restenosis by approximately 4%.”

Given the invasive nature of this treatment and the severe risks, as noted by Fiorella and colleagues, a well designed, well conducted randomized controlled trial is needed. The need for a randomized controlled trial was noted by Derdeyn and Chimowitz (2007) who stated: “At present, however, there is no level 1 evidence to support angioplasty and stenting for patients who have symptomatic intracranial atherosclerotic disease. Case series suggest that the safety and stroke risk reduction of this procedure may provide a benefit, particularly with self-expanding stent technology. A randomized, controlled trial is needed to prove the efficacy of this therapy.” Kallmes and Cloft wrote: “We, the community of physicians, really have to continue to ponder what the real value of Wingspan[®] is, and we must demand more data about safety and efficacy relative to other treatment options.”

CMS believes the evidence is promising and strongly encourages the development and completion of randomized controlled trials and currently covers PTA and stenting for the treatment of intracranial artery stenosis greater than or equal to 50 percent in patients with atherosclerotic disease when furnished in accordance with the FDA-approved protocols governing Category B IDE clinical trials. There is a newly funded clinical trial titled “Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS)” designed to determine health outcomes comparing optimal medical therapy to stenting and includes a 2 year mean follow-up. This randomized trial is expected to provide solid evidence on this intervention. Additional non-IDE trials would provide useful evidence as well and, in previous NCDs, we have covered research studies under the concept “Coverage with Evidence Development (CED).” However, as outlined in our Guidance Document on Coverage with Evidence Development, the Coverage with Study Participation (CSP) form of CED is applicable only for items and services where the medical evidence is not adequate for coverage under section 1862(a)(1)(A). In our existing NCD, 20.7.B.5, coverage exists under §1862(a)(1)(A) for beneficiaries in certain IDE trials, preventing any further expansion for these individuals under section 1862(a)(1)(E). Therefore we are proposing to make no change to the current coverage limited to Category B IDE trials. To further clarify based on these findings, CMS is not extending coverage to hospitals that are not conducting FDA-approved Category B IDE clinical trials and any use of intracranial stenting outside an IDE clinical trial would be non-covered.

IX. Summary

The Centers for Medicare and Medicaid Services (CMS) has reviewed the evidence for intracranial stenting and angioplasty for the patients with intracranial atherosclerotic disease (ICAD), who are medically refractory to therapy in intracranial vessels with $\geq$ 50% artery lumen stenosis that are accessible to the system. We propose to make no change to section 20.7 of the National Coverage Determination Manual titled “Percutaneous Transluminal Angioplasty” (PTA).

We are requesting public comments on this proposed determination pursuant to §1862(l) of the Social Security Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of an illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance of unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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[2] http://www.cms.hhs.gov/manuals/downloads/ncd103c1_Part1.pdf

[3] http://ww.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm

[4] http://www.fda.gov/cdrh/pdf5/h050001a.pdf

[5] http://www.fda.gov/cdrh/ode/hdeinfo.html

[6] Fiorella, et al. (2007) and Henkes, et al. (2005)

[7] Chimowitz, et al. (1995 and 2005)

[8] Henkes, et al. (2005) and Fiorella, et al. (2007)

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[11] Marks, et al. (2006)

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